NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

POLYVINYL ALCOHOL

(Molecular Weight ≈24,000)

(CAS NO. 9002-89-5)

IN FEMALE B6C3F$_1$ MICE

(INTRAVAGINAL STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

May 1998

NTP TR 474

NIH Publication No. 98-3964

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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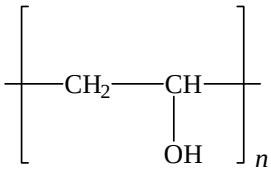
CONTENTS

ABSTRACT



POLYVINYL ALCOHOL

CAS No. 9002-89-5

Chemical Formula: $(C_2H_4O)_n$ Molecular Weight: approximately 24,000

Synonyms: Ethenol homopolymer, PVA
Trade names: Akwa Tears, Alcotex, Alvyl, Aracet, Cipoviol, Covol, Elvanol, Ethenol, Gelvatol, Gohsenol, Ivalon, Kuralon, Kurare, Lemol, Liquifilm, Mowiol, Polydesis, Polysizer, Polyvinol, Polyviol, Poval, Resistoflex, Rhodoviol, Sno Tears, Solvar, Sumitex, Vibatex, Vinacol, Vinalak, Vinarol, Vinarole, Vinavilol, Vinol, Vinylon

Polyvinyl alcohol is produced primarily for use in textile sizing, adhesives, polymerization aids, and paper coatings. It is also used in surgical drapes, towels, and gauze sponges; protective gloves; cosmetic formulations; topical ophthalmic preparations; plastic sponge implants for reconstructive surgery; and intravaginal contraceptive foam and film. In addition, polyvinyl alcohol is used with magnesium sulfate to dilate the cervix of women prior to induction of labor. It is estimated that hundreds of thousands of women in the United States use an intravaginal product containing polyvinyl alcohol each year. The Food and Drug Administration nominated low-viscosity polyvinyl alcohol for a 2-year study because of concern about the lack of information about the long-term toxic and carcinogenic effects by the intravaginal route. Female B6C3F$_1$ mice received polyvinyl alcohol (approximately 99% pure) in deionized water by intravaginal administration for 30 days or 2 years.

30-DAY STUDY IN MICE

Three groups of 50 female B6C3F$_1$ mice were used in this intravaginal study. The vehicle control group received only 20 μL of a deionized water vehicle. The other two groups each received 20 μL of 25% polyvinyl alcohol in deionized water. Animals in one dose group were returned to their cages after dosing; animals in the other dose group were restrained in a vertical nose-down position in restraint bags for several minutes after dosing. Animals were dosed daily for 30 consecutive days. All mice survived to the end of the study. The final mean body weights and body weight gains of dosed mice were similar to those of the vehicle control group. Abnormalities noted in the vaginal area after dosing included vaginal plugs, secretions, and swelling. These vaginal changes were minimal to mild and occurred in vehicle controls as well as in dosed mice. Restraint of mice after dosing appeared to eliminate vaginal secretions but increased both the incidence of vaginal irritation

and the severity of vaginal opening swelling. At necropsy, mildly enlarged uterine horns were observed in 10 vehicle control mice, three 25% mice, and seven 25% (restrained) mice. No chemical-related lesions were observed.

2-YEAR STUDY IN MICE

Three groups of 100 female B6C3F$_1$ mice were used in this intravaginal study: an untreated control group, a vehicle control group receiving 20 μL deionized water vehicle only, and a dosed group receiving 20 μL 25% polyvinyl alcohol in deionized water. Animals were dosed 5 days per week, excluding holidays, for 104 to 105 weeks.

Survival, Body Weights, and Clinical Findings

Survival of dosed mice was similar to that of the two control groups. The final mean body weight of vehicle control mice was less than that of the untreated control group. The mean body weights of the dosed mice were less than those of the untreated controls from week 17 until the end of the study. The only clinical finding was vaginal irritation, observed in six mice in the vehicle control group and 11 mice in the dosed group.

Pathology Findings

No neoplasms or nonneoplastic lesions related to chemical treatment were observed. The incidences of reproductive tract nonneoplastic lesions in the dosed group did not differ significantly from those in the vehicle control group; similarly, the incidences of reproductive tract nonneoplastic lesions in the vehicle control group did not differ significantly from those in the untreated control group.

CONCLUSIONS

Under the conditions of this 2-year study, there was *no evidence of carcinogenic activity** of polyvinyl alcohol (molecular weight approximately 24,000) in female B6C3F$_1$ mice administered 20 μL of a 25% solution intravaginally. There were no neoplasms or nonneoplastic lesions considered related to treatment with polyvinyl alcohol.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 10.

Summary of the 2-Year Carcinogenesis Study of Polyvinyl Alcohol in Female B6C3F$_1$ Mice

Doses	Untreated control, vehicle control receiving 20 μL deionized water only, and dosed group receiving 20 μL 25% polyvinyl alcohol in deionized water
Body weights	Vehicle control and dosed groups slightly less than untreated control group
2-Year survival rates	47/100, 51/100, 61/100
Nonneoplastic effects	None
Neoplastic effects	None
Level of evidence of carcinogenic activity	No evidence

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on polyvinyl alcohol on 12 December 1996 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 12 December 1996, the draft Technical Report on the toxicology and carcinogenesis studies of polyvinyl alcohol received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. A. Radovsky, NIEHS, introduced the toxicology and carcinogenesis studies of polyvinyl alcohol by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on the lack of compound-related neoplasms or nonneoplastic lesions in female mice. The proposed conclusion was *no evidence of carcinogenic activity* in female B6C3F$_1$ mice. No neoplasms or nonneoplastic lesions were considered related to treatment with polyvinyl alcohol.

Dr. Russo, a principal reviewer, agreed with the proposed conclusions. She had concerns about the lack of testing in the rat and not having more than one dose. This was in view of studies reporting development of sarcomas at the site of subcutaneous implants of polyvinyl sponges in rats that led the International Agency for Research on Cancer to recommend further studies in animals. Dr. Russo wondered if the chemical could be administered in a sponge or tampon. Dr. Radovsky said the 3′-azido-3′-deoxythymidine (AZT) studies had shown the mouse to be susceptible to developing vaginal neoplasms. She said the possibility of using a pessary or tampon could be considered in a future study.

Dr. Taylor, the second principal reviewer, agreed with the proposed conclusions. He said it would have been of merit to have developed innovative ways to administer higher doses. Dr. Radovsky said the problem with handling of the 25% solution of polyvinyl alcohol was not so much solubility as viscosity. The dose used was the maximum concentration that could be consistently administered with the available dosing equipment.

Dr. W. Allaben, Food and Drug Administration (FDA), said that the FDA was involved in the study design and the agency thought the information needed was obtained in spite of the technical difficulties. Dr. Goldsworthy asked whether Glaxo-Wellcome, in its studies of AZT in rats, observed similar responses with systemic versus intravaginal administration. Dr. Radovsky replied that vaginal neoplasms were induced when AZT was administered by oral gavage or vaginal administration. Dr. Tyson asked whether there was any leakage after intravaginal administration. Dr. Radovsky said there was some, but it was not quantifiable. Dr. H. Matthews, NIEHS, reported that his group studied disposition of radiolabeled polyvinyl alcohol in the rat using measures to avoid ingestion through grooming. He said there was very slight absorption without bioaccumulation after either single or multiple doses.

Dr. Russo moved that the Technical Report on polyvinyl alcohol be accepted with revisions discussed and the conclusions as written for female mice, *no evidence of carcinogenic activity*. Dr. Taylor seconded the motion, which was accepted unanimously with eight votes.